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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/245,025	02/05/1999	GARY F. GERARD	0942.4330003	4443

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EXAMINER
NASHED, NASHAAT T

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/245,025	Applicant(s) Gerard et al.
	Examiner Nashaat T. Nashed	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 9, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *117-148, 150-156, 158-164, 166-175, and 177-213* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *117-119* is/are allowed.

6) ☒ Claim(s) *120-148, 150-156, 158-164, 166-175, and 177-213* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *25*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The application has been amended as requested in the communication filed September 9, 2002. Accordingly, claims 119, 120, 126, 134, 140, 148, 150-154, 156-162, 164, 166-170, 175, 177-181, 183-188, 190-195, 197, 199-202, and 207-212 have been amended.

Claims 117-213 are pending. Claims 149, 157, 165, and 176 are withdrawn from further for being drawn to non-elected subject matter, and claims 117-148, 150-156, 158-164, 166-175 and 177-213 are under consideration in this Office action.

Since the specification reference specific amino acid residues from supposedly an amino acid sequence without identifying the amino acid sequence with a sequence identification number, see for example page 57, lines 11 and 12, and page 26, line 3. The reference to data bases accession number such as that on page 73, lines 14 and 15 is improper references to amino/nucleic acid sequences because the accession numbers can be changed by the data base without ever reverencing the old accession numbers. The previously mention non-compliance with the sequence rule are intended to be an examples and not as an exhaustive list of non-compliance with the sequence rules. Applicants are required to bring their application to full compliance with the sequence rules.

Applicants appear to disagree with examiner objection on the ground that 37 CFR § 1.821(a), "sequences with fewer than four specifically defined nucleotides or amino acids ...".

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. The examiner truly does not understand this disagreement and its ground. On page 57 for example, the specification describes the mutation of specific amino acid residues from what the examiner presumed a specific amino acid sequence. Position 450 of an RT refers to a specific amino acid residues in a specific RT which is not identified by the specification. Also, Glu484 and Asp505 are presumed to be specific amino acid residues in a specific RT sequence. Without identifying the sequence from which Glu484 and Asp505 are originated, the specification is incomprehensible. Applicant must comply with the sequence rule with regard to the specific amino acid residues in the specification.

Claims 148, 150-156, 158-164, 166-175, and 177-182 are objected to under 37 CFR § 1.75(d)(1) as being in improper form because the claim states an improper Markush groups. Compounds included within a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (See MPEP § 803.02.) The specification defines the abbreviation ASLV reverse transcriptase as any reverse transcriptase from any one of the viruses listed on page 4, lines 1-10, which defines a Markush group. The various members of the Markush group

in the claims are different chemical compound and do not share a common structural feature required for the stated utility, i. e., the reverse transcriptase activities.

In response to the above objection to the claims, Applicants argue that the Markush group is proper because they are related to ASLV RTs and subunits thereof which have reverse transcriptase activity.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. Applicants have not considered the teaching of MPEP § 803.02 which has two requirements. The first requirement is a common function and the second is a common structural feature required for the activity. In the instant claims, the members of the Markush group are all reverse transcriptases, but the specification fails to teach a specific structural feature required for the reverse transcriptase activity and common among all the members of the Markush group. In fact, the specification fails to teach any structure features for any of the reverse transcriptase and the scientific logic of making a particular mutation in order to remove or minimize the RNase H activity. Thus, the objection remains proper.

Claims 120-124, 126-129, 134, 136-138, 140-143, 150, 158, 166, 177, 184, 198, and 208 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The parent claims are drawn to compositions of viral reverse transcriptase, the wild-type. Claims 120-124, 126-129, 134, 136-143, 150, 158, 166, 177, 184, 198, and 208 expand the scop of the claim from which they depend to include mutants and fragments.

In response to the above objection to the claims, Applicants argue that the examiner has read a limitation in the independent claims which are not present in the claims.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. The independent claims are clearly drawn to viral reverse transcriptase. One of ordinary skill in the art would understand the phrase "viral reverse transcriptase" as the wild-type enzyme, i. e., isolated from its natural source. The phrase does not include variants or mutant of said viral reverse transcriptase. The claims remain objected to for the reasons stated above.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 120, 121, 126-148, 150-156, 158, 159-175, and 177-213 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the prior Office action, paper number 14.

In response to the above rejections, Applicants argue that a deposited *E. coli* containing a plasmid comprising DNA encoding AMV RT α- and β-subunits, a deposit comprising a DNA encoding AMV RT β-subunit (Rnase H^-), and similar deposits for the RSV RT. They further argue that the mature β-subunit can be generated by inserting a stop coldone in the place of the "p4" subunit cleavage site, and the sequence of ASLV are highly conserved among the reverse transcriptase. Also, Applicants argue that claims 121 and 135 are fully supported by the application.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. Applicants appear to argue an enablement rejection, but this rejections are directed to a lack of written description of the claimed invention. While the deposited biological materials may overcome an enablement issues, they are no substitute for a proper description of the claimed invention. It is untrue that retroviral sequences are highly conserved. In fact, several known sequences for HIV-1 RT are known in the prior art. Thus, indicating that an amino acid residue number XX of AMV-reverse transcriptase without identifying the sequence may or may not exist in another AMV RT from a different source than that of the applicants. Similarly, the problem would be even further magnified, if the reverse transcriptase is from a different retroviral. The specification has not identified any sequences of RT that can be used as a standard amino acid sequence for numbering purposes. Also, it has not taught any conserved amino acid residues among all reverse transcriptase or those required for the various activities. The specification merely identify a single residue(s) from a specific RT without even explaining the structure bases for such a mutation. Tables 1 and 2 in the specification show increase cDNA produce upon the addition of other RT's. That would be support a claim for a composition comprising more than one RT, but the instant claims are directed to RT composition comprising RT's with different pausing sites. Thus, since the Applicants have not taught the various posing sites, one of ordinary skill in the art would recognize that the applicant were not in position of the claimed composition at the time the application was filed. The results in Tables 1 and 2 may have other explanation for increasing the yield of cDNA than having a different posing sites. Finally, while applicants amended claims 148, 156, 164,

175, 183, 190, 197, and 207 to recite a "polymerase activity", the unite of activity is still not defined in the specification. Thus, the claims remain rejected.

Claims 117-148, 150-156, 158-164, 166-175 and 177-213 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

The phrases "ASLV reverse transcriptase" in claims 120, 126 134, 140, 148, 150-156, 158-164, 166-171, 175, 177-182; "specific activity ..... units per milligram" in claims 148, 151-156, 159-162, 164, 167-170, 178-181, 185-188, 190, 192-195, 197, 199-202, 207, and 209-212; and "one or more subunits" in claims 120, 126, 134, 140, 150, 158, 166, 177, 184, 191, 198, and 208 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired for the reasons set forth in the prior Office action, paper number 19.

In response to the above rejections, Applicants acknowledged that the phrase "ASLV reverse transcriptase" include, but not limited to the reverse transcriptases in the specification at pages 3-4, and argue that the sequences and function of ASLV subunits are highly conserved and refer to the specification on page 73, lines 13-14:

> "The RSV RT and AMV RT genes are related (GenBank J02342, ...). These genes code for identical sequence of amino acids over short distance of Rnase H region."

Also, applicant argue that claims 148, 156, 164, 175, 183, 190, 197, and 207, and their respective dependent claims to recite a "polymerase specific activity" further clarify the claims.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. Applicants appear to concede that the phrase ASLV is indefinite as they indicate that the phrase is not limited to the RT's listed in the specification on page 3-4. Applicants arguments seems to contradict the specification because the specification on page 73, lines 13-14 indicate that the sequences are highly conserved over short distance of the Rnase domain. Clearly, the specification have not identified those short distances conserved sequences. So, the reference to sequence homology is referring to a small segment of RT's and does not refer to global sequence homology which would guide an ordinary skill in the art in defining the limitation and boundaries of the phrase "ASLV".

With regard to the amendment of claims 148, 156, 164, 175, 183, 190, 197, and 207, and their respective dependent claims, the amended claim remain indefinite because the AMV RT has two known polymerase activities each of which is assayed by deferent

substrate and the unit of activity is defined in different terms. The activities are: (1) RNA-dependent DNA-polymerase activity which is described on page 99, second paragraph; and (2) DNA-dependent DNA-polymerase activity. Limiting the claims to RNA-dependent DNA-polymerase activity would lead to vacating this rejection.

Regarding the phrase "one or more subunits", while the homodimers are known to be enzymatically active, it is a daunting task to demonstrate the enzymatic activity of a monomer subunit. The specification shows enzymatic activities for homodimer and heterodimers. Also, the specification have not shown any catalytic activity attributed to a trimer or tetramer.

Applicants contend that the term "βp4" subunit is defined as an ASLV subunit which may be processed to produce the mature enzyme. Now, the examiner is truly confused. In most retroviruses, such as AMV and HIV-1 and 2, there is no gene encoding the mature β subunit or "βp4" subunit which can be processed further to something else. The primary product of the retroviral genome is a polyprotein which is processed primarily to the α-subunit which is further processed to the β-subunit. The translation "βp4" subunit RT is a mutant or truncated β-subunit which is structurally undefined.

Applicants contend that the term "reduced" and "substantially reduced" are clearly described in the specification on page 33, lines 12-23. While the term is "substantially reduced" is defined, the phrase"reduced" is not. The standard by which the activity is "reduced" or "substantially reduced" relative to is not stated in the specification. Amending the claims to reflect that the Rnase activity is "substantially reduced relative to the wild-type enzyme" would overcome this rejections.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 148, 150-156, 158-164, 166-171, 175, 177-203, 207-213 are rejected under 35 U.S.C. § 102(b) as being anticipated by Soltis *et al.* (see IDS: Proc. Natl. Acad. Sci. U. S. A. **1988**, 85, 3372-3376) for the reasons set forth in the prior Office action, paper number 19.

Claims 148, 150-156, 158-164, 166-171, 175, 177-203, and 207-213 are rejected under 35 U.S.C. § 102(b) as being anticipated by Yu (see IDS Reference: AR-26) for the reasons set forth in the prior Office action, paper number 19.

Claims 148, 150-156, 158-164, 166-171, 175, 177-203, 207-213 are rejected under 35 U.S.C. § 102(b) as being anticipated by the fact that AMV- and M-MulV-reverse transcriptase are commercially available (see IDS Reference: AT-19).

Claims 148, 150-156, 158-164, 166-175, and 177-182 are rejected under 35 U.S.C. § 102(b) as being anticipated by U. S. Patent 5,244,797 ('797, Kotewicz *et al.*).

In response to the above rejections, Applicants argue that under 35 U. S. C. § 102(b), a claim is expressly or inherently disclosed in a single prior art reference. Since such a burden has not been met, the rejections are not improper.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. First, a specific activity is an intrinsic property of a purified enzyme. Applicants have not provided any evidence to support that their claimed enzyme preparation is different from those of the prior art. Second, since the claims do not state specifically the polymerase activity in the claim, the examiner assumed that the claim reads on any preparation of AMF RT having any polymerase activity. In order for applicants to over come these rejections, they must distinguish their claimed enzyme composition from those of the prior art of record.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 148, 150-156, 158-164, 166-175, 177-213 are rejected under 35 U.S.C. § 103 as being unpatentable over either Soltis *et al.* in view of the state of the art at the time of the application was filed as exemplified by Chattopadhyay *et al.* [IDS: Protein Expression and Purification 3, 151-159 (1992)] for the reasons set forth in the prior Office action, paper number 19.

Claims 148, 150-156, 158-164, 166-175, 177-213 are rejected under 35 U.S.C. § 103 as being unpatentable over the fact that AMV- and M-MuLv-reverse transcriptase are commercially available from Boehringer Mannheim Biochemical and U. S. Biochemical in view of the state of the art at the time of the application was filed as exemplified by Chattopadhyay *et al.* [IDS: Protein Expression and Purification 3, 151-159 (1992)] for the reasons set forth in the prior Office action, paper number 19.

In response to the above rejections, Applicants argue that the examiner has a burden of establishing a *prima facie* case of obviousness because the claims are drawn specifically to RT's having a specific polymerase activity of at least 30,000 units which is not taught or suggested in the prior art.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. First, the specific activity is an intrinsic property of the claimed RT composition. Neither the specification or applicant argument show any unexpected results. The prior art teach several known genes known for retroviral reverse transcriptase and several of these enzymes are commercially available from several sources. The ordinary skill in the art would have had the skills and the knowledge as well as the prior art to express in a host system or buy the desired RT, and purify the RT to any desired specific activity for the polymerase activity of choice. It should be noted that any well defined specific activity has an upper limit which is reached when the enzyme is purified to homogeneity. The ordinary skill in the art would have had the confidence and reasonable expectation of success because of his/here experience in expressing enzymes in general and in particular, DNA-polymerases including reverse transcriptase. Thus, a *prima facie* case of obviousness has been established.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 148, 150-156, 158-164, 166-175, and 177-213 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,244,797 (797) for the reasons set forth in the prior Office action, paper number 19.

Claims 148, 150-156, 158-164, 166-175, and 177-213 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84 of U.S. Patent No. 6,063,608 (608) for the reasons set forth in the prior Office action, paper number 19.

In response to the above rejections, Applicants argue that the claims are clearly not obvious over the claims of the patents because the claims of the instant application are ASLV reverse transcriptase and AMV reverse transcriptase.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. The claims of the instant application are directed to ASLV RT comprises one or more ASLV α-subunit, one or more β-subunit, and one or more βp4 subunit, or combination thereof. βp4-subunit is a modified subunit having a reduced or no Rnase H activity as being claimed in 608 and 797 patents. Once again, the 30,000 unit of polymerase activity is not defined by the claim as what kind of polymerase activity, and it would an intrinsic property of the claimed invention of the RT of the 608 and 797 patents. Applicants have not distinguish their claimed compositions from those of the patents. Applicant should be reminded that AMV RT and modified AMV RT with reduced or no Rnase activity is within the definition of ASLV RT. Thus, the claims are obvious variants of the claimed inventions.

Claims 117-119 are allowed over the prior art of record.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nashaat T. Nashed, Ph. D.
Primary Examiner